Health Based Guidance for Air
Environmental Impacts Analysis Unit, Environmental Health Division
651-201-4899

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Air Toxicological Summary for: 1-Bromopropane

CAS: **106-94-5**
Synonyms: n-propyl-bromide

Air Exposure Durations:
Acute - dosing duration 24-hours or less
Short-term - repeated dosing for more than 24-hours, up to approximately 30 days
Subchronic - repeated dosing for more than 30 days, up to approximately 8 years (10 percent of a lifespan in humans; more than 30 days up to approximately 90 days in typical laboratory rodent species)
Chronic = repeated dosing for more than approximately 8 years (10 percent of a life span in humans; more than approximately 90 days in typical laboratory rodent species)

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = 100 µg/m^3

$$= \frac{\text{(Point of Departure (POD), mg/m}^3\text{)}}{\text{(Uncertainty Factors (UF))}}$$

$$= \frac{\text{(32.6 mg/m}^3\text{)}}{\text{(300)}}$$

= 0.109 mg/m^3 rounded to 100 µg/m^3

Reference Concentration:	HEC/Total UF = 0.11 mg/m^3
Source of toxicity value:	MDH 2022; based on WIL Research 2001 (animal study) aci; EPA TSCA 2020
POD and Critical Effect:	$BMDL_{01}$ = 130 mg/m^3 (25.9 ppm); post-implantation loss in F0 female rats
Human Equivalent Concentration (HEC):	32.6 mg/m^3)
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	UF_A was set to a full 10 as there is no PBPK model for 1-BP to account for the interspecies extrapolation using rodent toxicokinetic data in order to estimate internal doses for a particular dose metric, further 1-BP is irritating to the respiratory tract and rodents exhibit physiological responses (i.e. reflex bradypnea) that differ from humans and may alter uptake due to hyper- or hypoventilation, resulting in decreased internal dose in rodents relative to the applied

	concentration; UF_H was set at 10 to protect sensitive human subpopulations; UF_{DB} of 3 is used to account for database deficiencies in developmental neurotox studies because the nervous system is critical endpoint for 1-bromopropane toxicity in humans and animals, it is reasonable to suggest that younger organisms, in which the nervous system is still developing, might be more susceptible to 1-bromopropane toxicity than mature individuals

Short-term Non-Cancer Health Based Value ($nHBV_{ST}$) = 30 µg/m³

$$= \frac{\text{(Point of Departure (POD), mg/m}^3\text{)}}{\text{(Uncertainty Factors (UF))}}$$

$$= \frac{\text{(84 mg/m}^3\text{)}}{\text{(3000)}}$$

$$= 0.028 \text{ mg/m}^3 = 30 \text{ µg/m}^3$$

Reference Concentration:	HEC/Total UF = 0.028 mg/m³
Source of toxicity value:	Determined by MDH 2022; based on Liu et al. 2009 (animal study)
POD and Critical Effect:	LOAEL = 252 mg/m³ (50 ppm); liver lobule degeneration and necrosis
Human Equivalent Concentration:	84 mg/m³ (16.7 ppm)
Total uncertainty factor:	3000
Uncertainty factor allocation:	UF_A was set to a full 10 as there is no PBPK model for 1-BP to account for the interspecies extrapolation using rodent toxicokinetic data in order to estimate internal doses for a particular dose metric, further 1-BP is irritating to the respiratory tract and rodents exhibit physiological responses (i.e. reflex bradypnea) that differ from humans and may alter uptake due to hyper- or hypoventilation, resulting in decreased internal dose in rodents relative to the applied concentration; UF_H was set at 10 to protect sensitive human subpopulations; a full UF_L 10 is retained for use of a LOAEL with a severe critical effect; UF_{DB} of 3 is used to account for database deficiencies in developmental neurotox studies because the nervous system is critical endpoint for 1-bromopropane toxicity in humans and animals, it is reasonable to suggest that younger organisms, in which the nervous system is still developing, might be more susceptible to 1-bromopropane toxicity than mature individuals

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 20 µg/m³

$$= \frac{\text{(Point of Departure (POD), mg/m}^3\text{)}}{\text{(Uncertainty Factors (UF))}}$$

$$= \frac{(2.3\ mg/m^3)}{(100)}$$

$$= 0.023\ mg/m^3 = 20\ \mu g/m^3$$

Reference Concentration:	HEC/Total UF = 0.023 mg/m^3
Source of toxicity value:	Determined by MDH 2019 or agency; based on Li et al. 2010 (human occupational study)
POD and Critical Effect:	LOAEL = 6.44 mg/m^3 (1.28ppm); mild neurological impairment (increased vibration sense threshold) in female workers
Human Equivalent Concentration:	2.3 mg/m^3
Total uncertainty factor:	100
Uncertainty factor allocation:	UF_H was set at 10 to protect sensitive human subpopulations; a UF_L of 3 was used as the critical effect is mild; UF_{DB} of 3 is used to account for database deficiencies in developmental neurotox studies because the nervous system is critical endpoint for 1-bromopropane toxicity in humans and animals, it is reasonable to suggest that younger organisms, in which the nervous system is still developing, might be more susceptible to 1-bromopropane toxicity than mature individuals

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 2 µg/m^3

$$= \frac{(\text{Point of Departure (POD), mg/m}^3)}{(\text{Uncertainty Factors (UF)})}$$

$$= \frac{(2.3\ mg/m^3)}{(1000)}$$

$$= 0.0023\ mg/m^3 = 2\ \mu g/m^3$$

Reference Concentration:	HEC/Total UF = 0.0023 mg/m^3
Source of toxicity value:	Determined by MDH 2019 or agency; based on Li et al. 2010 (human occupational study)
POD and Critical Effect:	LOAEL = 6.44 mg/m^3 (1.28 ppm); mild neurological impairment (increased vibration sense threshold) in female workers
Human Equivalent Concentration:	2.3 mg/m^3
Total uncertainty factor:	1000
Uncertainty factor allocation:	UF_H was set at 10 to protect sensitive human subpopulations; a UF_L of 3 was used as the critical effect is mild; A full UF_S 10 was used for subchronic to chronic duration; UF_{DB} of 3 is used to account for database deficiencies in developmental neurotox studies because the nervous system is critical endpoint for 1-bromopropane toxicity in humans and

animals, it is reasonable to suggest that younger organisms, in which the nervous system is still developing, might be more susceptible to 1-bromopropane toxicity than mature individuals

Cancer Health Based Value/Risk Assessment Advice = 6 µg/m^3

Cancer classification:	Likely to be carcinogenic in humans (EPA 2005, EPA TSCA 2020); Possibly carcinogenic to humans (IARC 2018)
Inhalation Unit Risk (IUR_{adj}):	1.55×10^{-6} (µg/m^3)$^{-1}$; Per MDH policy (MDH 2020), ADAF are applied to the IUR to protect against early-life sensitivity to 1-BP exposure
Source of IUR:	MDH 2023; based on NTP 2011
Tumor site(s):	skin tumors

Cancer ADAF and HBV Calculations:

IUR_{adj} = IUR x [(2 yrs x 10) + (14 yrs x 3) + (54 yrs x 1)] / 70 yrs

$IUR_{adj} = 9.34 \times 10^{-4}$ (mg/m^3)$^{-1}$ x 1.657

$IUR_{adj} = 1.55 \times 10^{-3}$ (mg/m^3)$^{-1}$

Cancer HBV = [additional lifetime cancer risk / IUR_{adj}] x 1000

Cancer HBV = [0.00001 / 1.55×10^{-3} (mg/m^3)$^{-1}$] x 1000 = 6.46 µg/m^3 = 6 µg/m^3

Volatile: Yes - average Henry's Law = $2.31e^{-6}$ atm-m^3/mol (EPA CompTox Chemicals Dashboard; accessed March 2023)

Summary of Guidance Value History:

MDH had previously derived noncancer HBVs in 2011 from rodent studies. An acute (1-hour exposure duration) HBV of 50,000 µg/m^3 was derived from a developmental rat study. The critical effect was reduced fetal weight based on a BMCL of 1534 mg/m^3. A subchronic (13-week duration) HBV of 4,000 µg/m^3 was derived from a rat study reporting neurological effects at a NOAEC of 1006 mg/m^3. A chronic (annual average duration) HBV of 20 µg/m^3 was derived from a rat study reporting non-neoplastic respiratory lesions at a LOAEC of 629 mg/m^3 (rat) and 314 mg/m^3 (mouse). No cancer value was derived in 2011.

The updated 2023 1-BP HBVs reflect MDH's 2020 revised exposure durations and incorporates different critical studies (rodent and occupational) and endpoints for each duration. The 2023 acute HBV is based on a severe developmental effect (post-implantation loss) with a point of departure (POD) substantively less than the 2011 POD and a final acute HBV 500 times less than the 2011 evaluation. The short-term HBV is based on rodent liver degeneration and necrosis, also a severe effect. A short-term duration was not part of

the 2011 evaluation. The 2023 subchronic and chronic HBVs are derived from the same occupational study resulting in neurological system disruption. Neurological toxicity is a known sensitive endpoint for 1-BP exposure. Generally, quality human studies are preferred to animal studies when deriving HBVs. The 2023 subchronic and chronic values result in HBVs that are 200 and 10 times lower, respectively, than previous 2011 values.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity	Respiratory
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]	Yes[6]

Comments on extent of testing or effects:

[1] In human studies, workers exposed to 1-BP showed trends for increased thyroid stimulating hormone and follicle stimulation hormone in female workers but, neither female estradiol nor male testosterone were significantly altered from 1-BP exposure ranging from 1 – 23 ppm. In rodents, subchronic 1-BP exposure resulted in necrosis to the adrenal cortex at a LOAEL of 500 ppm and increased relative weight of the adrenal gland at 50 ppm; however, exposure to higher concentrations did not show a clear dose-response relationship. 1-BP exposure-related changes were not reported in other subchronic rat studies for adrenal or pituitary weight following intermittently exposed to concentrations up to 1,000 ppm.

[2] There is limited evidence for immune effects of 1-BP in animal studies. 1-BP is reported to decreased IgM plaque-forming response to immunization with sheep red blood cells in splenocytes harvested from female rodents following subchronic inhalation exposure at a LOAEL of 125 ppm in mice. Effects in rodents also included decreases in T cells and increases in natural killer cells in the spleen and reduced splenic cellularity and decreased absolute spleen weight in mice following subchronic 1-BP exposure.

[3] Strong evidence supports fetal development as a sensitive critical effect of 1-BP exposure in animal studies. Per EPA TSCA 2020, the current database consists of developmental toxicity testing that shows severe effects resulting from prenatal exposure during gestation and postnatal exposure studies showing adverse developmental effects that manifest at various stages of development, and span across multiple generations. Overall, the general consistency of findings indicative of impaired development across species, as reported in multiple studies from independent laboratories are taken as evidence of a causative association between 1-BP exposure and developmental toxicity. Reported adverse developmental effects following 1-BP exposure include dose-related decreases in live litter size, postnatal

survival, and pup body weight, brain weight and skeletal development at concentrations ranging from 100 – 500 ppm.

[4] Strong evidence supports reproductive toxicity following 1-BP exposure. Per EPA TSCA 2020, quantitative and qualitative evidence of 1-BP reproductive toxicity in F0 males include decreases in sperm motility, changes in normal sperm morphology, decreases in mating and fertility indices, and decreases in epididymal, prostate, and seminal vesicle weights following 1-BP (whole-body) inhalation exposures ranging from 100-500 ppm. Evidence of reproductive toxicity in F0 females include decreased numbers of corpora lutea, antral follicles, and implantation sites. Other reported reproductive effects in females include a significant upward trend in increased estrous cycle length, and evidence of mating without delivery. Reported impairments in male and female reproductive function resulted in a 48% reduction in fertility at 500 ppm and complete infertility at 750 ppm in F0 mating pairs. Further animal data shows adverse effects to male and female reproductive systems including sperm damage, altered hormone concentrations, altered estrous cycles, and altered reproductive development following exposure concentrations ≥50 ppm.

[5] Evidence from both human and animal studies strongly support the nervous system is a sensitive target of 1-BP exposure. In animal studies, the severity of neurotoxicity produced by 1-BP depends on the concentration and duration of exposure. A lower concentration exposure can elicit a response following longer exposure periods. Animal studies using concentrations of ≥1000 ppm report ataxia progressing to severely altered gait, hindlimb weakness to loss of hindlimb control, convulsions, and death. Neuropathological changes including peripheral nerve degeneration, myelin sheath abnormalities, and spinal cord axonal swelling can occur at concentrations of 400 – 1000 ppm. Rodent behavioral tests (grip strength, foot splay, hang time, gait, motor activity, maze performance) provide sensitive dose-response data that was significantly altered at concentrations as low as 50 – 100 ppm.

Human occupational studies confirm the nervous system is a sensitive 1-BP target. Per EPA TSCA 2020, Clinical signs of neurotoxicity (including headache, dizziness, weakness, numbness in lower extremities, ataxia, paresthesia, and changes in mood) and motor and sensory impairments were noted in the case reports of workers occupationally exposed to 1-BP for 2 weeks to 3 years at estimated concentrations exceeding averages of 100 ppm, and in industrial surveys with average exposures greater than 81 ppm (ranging from 2 weeks to 9 years). Cross-sectional studies of Chinese workers reported increased distal latency and decreased sural nerve conduction velocity in female workers. Statistically significant decreased vibration sense in toes was observed across all exposure groups (0.07 – 106.4 ppm) compared to controls.

[6] Limited evidence is available for respiratory effects of 1-BP in humans. Occupational studies including short-term to chronic durations report 1-BP can cause mild respiratory irritation at concentrations ranging from 1 – 171 ppm. Workers exposed to 1-BP for more than three months reported sore throat, hoarseness, and/or sinus irritation at 1-BP concentrations ranging from 60 – 261 ppm.

Rodent study showed respiratory tract lesions in rats and mice at greater than 125 or 62.5 ppm, respectively in chronic exposures. Male rats exposed to ≥500 ppm 1-bromopropane for 16 days showed nasal lesions, including minimal necrosis of the respiratory epithelium and suppurative inflammation. At concentrations ≥500 ppm histopathological changes in the nose in mice were observed and histological changes in the lungs were observed at ≥125 ppm after 17 days.

Resources Consulted During Review:

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US EPA TSCA. 2022. Risk Evaluation for 1-Bromopropane – Unreasonable Risk Determination. https://www.epa.gov/system/files/documents/2022-12/1-BP_Final%20Revised%20RD_12-12-22.pdf

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